REMARKS

This paper is supplemental to the Amendment filed November 10, 2005, which was responsive to the last Office Action on the merits, dated April 21, 2005.

Claims 1 and 10-38 were previously pending in the application, of which 1, 10 and 19-33 were under examination. Upon entry of this paper into the file, claims 16-18, 34-38, and 44-46 are now cancelled, and new claims 55-57 are introduced to replace the cancelled claims. The new claims fall within the group under examination.

Accordingly, claims 1, 10-16, 19-33, 39-43, and 47-57 are now pending, with claims 11-15 withdrawn from examination. Further consideration and allowance of the application is respectfully requested.

Interview summary:

The undersigned wishes to express his appreciation to Examiner Susan Ungar for a very helpful and productive telephone consultation earlier today. Suitable claim wording and support for the claim wording in the specification were discussed.

The amendments and remarks made in this submission are believed to resolve all previously made rejections of the claims.

Amendments

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the claim as amended here may be found throughout the specification and the claims as previously presented. The following parts of the disclosure as filed were discussed during the interview:

- Immunogenic amino acid sequences of at least 10 amino acids of SEQ. ID NO:2 — page 64, lines 20-24.
- Immunogenic amino acid sequences of at least 20 or at least 50 amino acids — original claims 6, 7, 8, and 9
- Nucleic acids comprising at least about 25, 100, or 200 bases of TRT encoding sequences — page 21, lines 15-18.

- Production of TRT peptides by polynucleotide expression for vaccine purposes — page 50, lines 29-33.
- Raising an immune response by delivery of vectors encoding the polypeptide of interest — page 90, lines 12-18.
- Altered codons selected to increase the rate of expression (new claim 56) — page 25, lines 20-23.

Other aspects of the claimed invention can be found throughout the specification, including the following:

- Chimeric molecules for eliciting hTRT antibody comprising an amino acid sequence of hTRT fused to another protein (claim 25) — page 64, lines 25-27.
- hTRT compositions without hTRT activity but with immunogenic properties (claim 43) — page 39, lines 1-11. Assays for hTRT activity: page 42, line 26 ff. Strategy for making hTRT without telomerase activity: page 47, line 25 to page 48, line 7; Examples 1 and 16.
- Viral sequences for replication and packaging (New claim 55) — Page 55, lines 30-33.

With regards to altering codons to increase the rate of expression (claim 56), applicants submit that this aspect of the invention can readily be put into practice by the skilled reader by reading the disclosure in the context of what was known in the art at the time of filing. Codon usage by tRNA in unicellular and multicellular organisms had been well known for over a decade (reviewed by T. Ikemura, Mol. Biol. Evol. 2:13-34, 1985). Algorithms were available at the time of filing to generate sequences with optimized codon usage, and expression vectors were often optimized to match the codon usage in the host cell — be it *E. coli,* yeast, or mammalian cells. A sampling of relevant abstracts is attached hereto. Issued U.S. Patents 5,736,131 (Bosch et al.) and 5,917,122 (Byrne) both have dependent claims to optimized codon usage, and both were filed before the priority hTRT application.

The amendments are made to obtain coverage for certain aspects of the invention that are of current commercial interest. Applicant reserves the right to introduce claims to subject matter previously claimed or described in the disclosure in this or any other application.

Many of the claims have been reworded in this Amendment without introducing any substantial new limitations. Accordingly, coverage is maintained for all equivalents of the subject matter in these claims for which applicant was previously entitled.

Double patenting

Possible double patenting issues were discussed during the telephone issue with respect to issued patents owned or co-owned by Geron Corporation The Examiner and the undersigned agreed there no double patenting of the invention claimed here compared with the claims in U.S. Patents 6,093,809 (ciliate telomerase) and 6,475,789 (telomerized cells).

Other potential double patenting issues will be addressed by applicants' representatives under separate cover.

Request for Rejoinder:

Claims 11-15 are method claims that depend from and incorporate the limitations of product claims in the group under examination. Applicant hereby requests that these claims be rejoined, upon determination that the product claims are patentable, in accordance with MPEP § 821.04. The other claims previously withdrawn from examination have been cancelled.

Request for Interview

Applicants respectfully submit that the amended claims comply with all the patentability requirements of Section 35 of the U.S. Code. Withdrawal of all previously made rejections and allowance of the application is respectfully requested.

In the event that the Examiner determines that there are other matters to be addressed, the undersigned hereby requests a further interview by telephone.

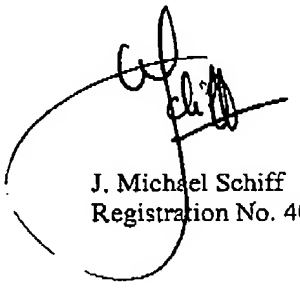
PATENT
USSN 10/044,692
TTC Docket 002640US
Geron Docket 018/213c

Fees Due

The Commissioner is hereby authorized to charge Deposit Account 07-1139 with the fees for the claims added in this Amendment, and any claims previously added that have not already been paid for.

Should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicants hereby petition for such relief, and authorize the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket numbers indicated above.

Respectfully submitted,



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1: Mol Biol Evol. 1985 Jan;2(1):13-34. Related Articles, Links

Codon usage and tRNA content in unicellular and multicellular organisms.

Ikemura T.

Department of Biophysics, Faculty of Science, Kyoto University, Japan.

Choices of synonymous codons in unicellular organisms are here reviewed, and differences in synonymous codon usages between Escherichia coli and the yeast Saccharomyces cerevisiae are attributed to differences in the actual populations of isoaccepting tRNAs. There exists a strong positive correlation between codon usage and tRNA content in both organisms, and the extent of this correlation relates to the protein production levels of individual genes. Codon-choice patterns are believed to have been well conserved during the course of evolution. Examination of silent substitutions and tRNA populations in Enterobacteriaceae revealed that the evolutionary constraint imposed by tRNA content on codon usage decelerated rather than accelerated the silent-substitution rate, at least insofar as pairs of taxonomically related organisms were examined. Codon-choice patterns of multicellular organisms are briefly reviewed, and diversity in G+C percentage at the third position of codons in vertebrate genes--as well as a possible causative factor in the production of this diversity--is discussed.

Publication Types:
- Review

PMID: 3916708 [PubMed - indexed for MEDLINE]

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1: Protein Eng. 1992 Dec;5(8):821-5. Related Articles, Links

Computer-aided gene design.

Libertini G, Di Donato A.

Department of Organic and Biological Chemistry, University of Naples, Federico II, Italy.

A computer program, which runs on MS-DOS personal computers, is described that assists in the design of synthetic genes coding for proteins. The goal of the program is the design of a gene which (i) contains as many unique restriction sites as possible and (ii) uses a specific codon usage. The gene designed according to the criteria above is (i) suitable for 'modular mutagenesis' experiments and (ii) optimized for expression. The program 'reverse-translates' protein sequences into degenerated DNA sequences, generates a map of potential restriction sites and locates sequence positions where unique restriction sites can be accommodated. The nucleic acid sequence is then 'refined' according to a specific codon usage to remove any degeneration. Unique restriction sites, if potentially present, can be 'forced' into the degenerated nucleic acid sequence by using 'priority codes' assigned to different restriction sequences.

PMID: 1287664 [PubMed - indexed for MEDLINE]

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1: Genc. 1993 Dec 22;136(1-2):323-8. Related Articles, Links

HIV1 integrase expressed in Escherichia coli from a synthetic gene.

Holler TP, Foltin SK, Ye QZ, Hupe DJ.

Department of Biochemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105.

Human immunodeficiency virus type 1 (HIV1) integrase is cleaved from the gag-pol precursor by the HIV1 protease. The resulting 32-kDa protein is used by the infecting virus to insert a linear, double-stranded DNA copy of its genome, prepared by reverse transcription of viral RNA, into the host cell's chromosomal DNA. In order to achieve high levels of expression, to minimize an internal initiation problem and to facilitate mutagenesis, we have designed and synthesized a gene encoding the integrase from the infectious molecular clone, pNL4-3. Codon usage was optimized for expression in Escherichia coli and unique restriction sites were incorporated throughout the gene. A 905-bp cassette containing a ribosome-binding site, a start codon and the integrase-coding sequence, sandwiched between EcoRI and HindIII sites, was synthesized by overlap extension of nine long synthetic oligodeoxyribonucleotides [90-120 nucleotides (nt)] and subsequent amplification using two primers (28-30 nt). The cassette was subcloned into the vector pKK223-3 for expression under control of a tac promoter. The protein produced from this highly expressed gene has the expected N-terminal sequence and molecular mass, and displays the DNA processing, DNA joining and disintegration activities expected from recombinant integrase. These studies have demonstrated the utility of codon optimization, and lay the groundwork for structure-function studies of HIV1 integrase.

PMID: 7916726 [PubMed - indexed for MEDLINE]

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1: Gene. 1997 Oct 15;199(1-2):293-301.

Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Codon optimization for high-level expression of human erythropoietin (EPO) in mammalian cells.

Kim CH, Oh Y, Lee TH.

Biotech Research Institute, LG Chem, Taejeon, South Korea.

Codon bias has been observed in many species. The usage of selective codons in a given gene is positively correlated with its expression efficiency. As an experimental approach to study codon-usage effects on heterologous gene expression in mammalian cells, we designed two human erythropoietin (EPO) genes, one in which native codons were systematically substituted with codons frequently found in highly expressed human genes and the other with codons prevalent in yeast genes. Relative performances of the re-engineered EPO genes were evaluated with various combinations of promoters and signal leader sequences. Under the comparable set of combinations, mature EPO gene with human high-frequency codons gave a considerably higher level of expression than that with yeast high-frequency codons. However, the levels of EPO expression varied, depending on the alternate combinations. Since the promoters and the signal leader sequences that we used are known to be equally efficient in gene expression, we hypothesized that the varied expression levels were due to the linear sequence between the promoter and the coding gene sequence. To test this possibility, we designed the EPO gene with hybrid codon usage in which the 5'-proximal region of the EPO gene was synthesized with yeast-biased codons and the rest with human-biased codons. This codon-usage hybrid EPO gene substantially enhanced the level of EPO transcripts and proteins up to 2.9-fold and 13.8-fold, respectively, when compared to the level reached by the original counterpart. Our results suggest that the linear sequence between the promoter and the 5'-proximal region of a gene plays an important role in achieving high-level expression in mammalian cells.

PMID: 9358069 [PubMed - indexed for MEDLINE]

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1: Biotechnology (N Y). 1991 Dec;9(12):1386-9. Related Articles, Links

Evaluation of foreign gene codon optimization in yeast: expression of a mouse IG kappa chain.

Kotula L, Curtis PJ.

Wistar Institute of Anatomy and Biology, Philadelphia, PA 19104.

We have optimized the codons in an immunoglobulin kappa chain gene to those preferred in the yeast Saccharomyces cerevisiae. The mutant and wild type kappa chain genes were each fused with a synthetic invertase signal peptide that also contained only yeast-preferred codons, and expressed in the F762 yeast strain. The use of yeast-preferred codons resulted in a more than 5-fold increase in the rate of synthesis and at least a 50-fold increase in the steady state level of protein.

PMID: 1367771 [PubMed - indexed for MEDLINE]

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1: Protein Expr Purif. 1998 Mar;12(2):185-8.

Related Articles, Links

Codon optimization of the gene encoding a domain from human type 1 neurofibromin protein results in a threefold improvement in expression level in Escherichia coli.

Hale RS, Thompson G.

Biomolecular Structure Unit, GlaxoWellcome R & D, Stevenage, United Kingdom.

An internal domain from the human type 1 neurofibromin has previously been expressed in Escherichia coli as a fusion with gluthathione S-transferase (GST). The expression level of this protein was lower than expected and so a gene was constructed using the distribution of codons found in highly expressed E. coli proteins. Codons were assigned using a Microsoft Visual Basic computer program to give a distribution similar to those found in genes which are highly expressed in E. coli. The optimized gene was then cloned back into the same GST fusion plasmid and it was found that the expression of soluble protein had increased threefold.

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